Exhibit II

THE MERCK MANUAL

SEVENTEENTH EDITION

CENTENNIAL EDITION

TRUAL
RMALITIES AND
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weight gain, oliguria, and breast fullness and pain. Neurologic and vascular symptoms include headache, vertigo, syncope, paresthesias of the extremities, easy bruising, and cardiac palpitation. Epilepsy may be aggravated. GI symptoms include constipation, nausea, vomiting, and changes in appetite. Pelvic heaviness or pressure and backache may occur. Acne, neurodermatitis, and aggravation of other skin disorders may also occur. Respiratory problems (eg, allergies, infection) and eye complaints (eg, visual disturbance, conjunctivitis) may worsen.

Tr atment

Treatment involves relief of symptoms. Fluid retention may be relieved by reducing sodium intake and using a diuretic (eg, hydrochlorothiazide 25 to 50 mg/day po), starting just before symptoms are expected. Diuretics promote sodium and water excretion but do not relieve all symptoms and may have no effect. Counseling may help the woman and her partner cope with PMS, and the woman's activities can be modified to reduce stress. For some women, hormonal manipulation is effective. Regimens include oral contraceptives; progesterone by vaginal suppository (200 to 400 mg/day) or by injection (5 to 10 mg IM in oil) for 10 to 12 days premenstrually; a long-acting progestin (eg, medroxyprogesterone acetate 200 mg IM q 2 to 3 mo); or a gonadotropin-releasing hormone agonist (eg, leuprolide 3.75 mg IM or goserelin 3.6 mg IM monthly) with low-dose estrogen-progestin "add-back" therapy to eliminate cyclic changes. Tranquilizers (eg, a benzodiazepine) may be used for irritability, nervousness, and lack of control, especially if patients cannot alter their stressful environments. Changing the diet (eg, increasing protein, decreasing sugars) and supplementing with vitamin B complex (especially pyridoxine, sometimes with magnesium) may help. Spironolactone, bromocriptine, and monoamine oxidase inhibitors are not beneficial. Selective serotonin reuptake inhibitors (eg, fluoxetine 20 mg po daily, sertraline 50 mg po daily) are the most effective drugs in the management of psychologic and physical PMS symptoms.

PRIMARY DYSMENORRHEA

(Functional Dysmenorrhea)

Cyclic pain associated with ovulatory cycles without demonstrable lesions affecting reproductive structures.

The pain is thought to result from uterine contractions and ischemia, probably mediated by prostaglandins produced in secretory endometrium; therefore, primary dysmenorrhea is almost always associated with ovulatory cycles. Contributing factors may include the passage of tissue through the cervix, a narrow cervical os, malposition of the uterus, lack of exercise, and anxiety about menses. This common disorder usually starts during adolescence and tends to decrease with age and after pregnancy.

Symptoms and Signs

Low abdominal pain is usually crampy or colicky but may be a dull constant ache and radiate to the lower back or legs. The pain may start before or with menses, tends to peak after 24 h, and usually subsides after 2 days. Sometimes endometrial casts (membranous dysmenorrhea) or clots are expelled. Headache, nausea, constipation or diarrhea, and urinary frequency are common; vomiting occurs occasionally. PMS symptoms (see above) may persist during part or all of the menses.

Treatment

A woman should be assured that her reproductive organs are normal. Many women do not need drugs, but for women with substantially bothersome symptoms, the most effective drugs are prostaglandin synthetase inhibitors (eg, ibuprofen, naproxen, mefenamic acid). A drug may be more effective if started 24 to 48 h before and continued 1 or 2 days after menses begins. If pain continues to interfere with normal activity, suppression of ovulation with low-dose estrogen-progesterone oral contraceptives is advisable. Antiemetics may be used. Adequate rest and sleep and regular exercise may help.

SECONDARY DYSMENORRHEA

(Acquired Dysmenorrhea)

Pain with menses caused by demonstrable pathology.

Endometriosis is a common cause of dysmenorrhea; adenomyosis may also cause it. A few women have an extremely tight cervical os (secondary to conization, cryocautery, or thermocautery); pain occurs when the uterus attempts to expel tissue through the os. A pedunculated submucosal fibroid or an endometrial polyp extruding from the uterus occasionally causes cramping pain. Pelvic inflammatory disease may cause diffuse continuous low abdominal pain that tends to increase with menses. Sometimes, a cause cannot be found.

Treatment

The first line of treatment is medical (eg, prostaglandin synthetase inhibitors, oral contraceptives, danazol, progestins). For management of endometriosis, see Ch. 239. If possible, the underlying disorder or anatomic abnormality is corrected, thus relieving symptoms. Dilation of a narrow cervical os may give 3 to 6 mo of relief (and allows diagnostic curettage if needed). Myomectomy, polypectomy, or dilation and curettage may be needed. Interruption of uterine nerves by presacral neurectomy and division of the sacrouterine ligaments may help selected patients. Hypnosis may be useful.

AMENORRHEA

Absence of menstruation—either because it never began or later ceased.

Amenorrhea is traditionally categorized as primary (menarche has not occurred by age 16) or secondary (menses has not occurred for ≥ 3 mo in women who have had menses), although often this distinction is not clinically useful. A functional approach is more helpful.

Etiology

Amenorrhea—except that occurring before puberty, during pregnancy or early lactation, and after menopause—is pathologic. Amenorrhea indicates failure of hypothalamic-pituitary-gonadal-uterine interaction to produce cyclic changes in the endome-